

PCT

From the INTERNATIONAL BUREAU

**NOTIFICATION OF THE RECORDING
OF A CHANGE**

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

HOWARD, Paul, Nicholas
Carpmaels & Ransford
43 Bloomsbury Square
London WC1A 2RA
ROYAUME-UNI

Date of mailing (day/month/year) 05 July 2000 (05.07.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference P018623WO	
International application No. PCT/GB99/00223	International filing date (day/month/year) 22 January 1999 (22.01.99)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

CEREBRUS PHARMACEUTICALS LIMITED
Oakdene Court
613 Reading Road
Winnersh
Wokingham RG41 5UA
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

VERNALIS RESEARCH LIMITED
Oakdene Court
613 Reading Road
Winnersh
Wokingham RG41 5UA
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Ingrid Aulich

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HOWARD, Paul, Nicholas
Carpmaels & Ransford
43 Bloomsbury Square
London WC1A 2RA
ROYAUME-UNI

Date of mailing (day/month/year)
31 August 1999 (31.08.99)

Applicant's or agent's file reference
P018623WO

International application No.
PCT/GB99/00223

IMPORTANT NOTIFICATION

International filing date (day/month/year)
22 January 1999 (22.01.99)

1. The following indications appeared on record concerning:

☒

the applicant

☐

the inventor

☐

the agent

☐

the common representative

Name and Address

CEREBRUS LIMITED
Oakdene Court
613 Reading Road
Winnersh
Wokingham RG41 5UA
United Kingdom

State of Nationality

GB

State of Residence

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Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

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the person

☒

the name

☐

the address

☐

the nationality

☐

the residence

Name and Address

CEREBRUS PHARMACEUTICALS LIMITED
Oakdene Court
613 Reading Road
Winnersh
Wokingham RG41 5UA
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒

the receiving Office

☐

the International Searching Authority

☒

the International Preliminary Examining Authority

☐

the designated Offices concerned

☒

the elected Offices concerned

☐

other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

H. Zhou

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

11 August 1999 (11.08.99)

International application No.

PCT/GB99/00223

Applicant's or agent's file reference

P018623WO

International filing date (day/month/year)

22 January 1999 (22.01.99)

Priority date (day/month/year)

23 January 1998 (23.01.98)

Applicant

ADAMS, David, Reginald et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

09 July 1999 (09.07.99)



in a notice effecting later election filed with the International Bureau on:

2. The election



was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P018623W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/ 00223	International filing date (day/month/year) 22/01/1999	(Earliest) Priority Date (day/month/year) 23/01/1998
Applicant CEREBRUS LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established by this Authority to read as follows:

AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 00223

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24-27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 24-27
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00223

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D205/04 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ✓	GB 872 447 A (LEPETIT S.P.A.) 12 July 1961 see the whole document	1, 2, 18, 23
A ✓	EP 0 194 112 A (ROBINS CO INC A H) 10 September 1986 see claims & US 4 956 359 A cited in the application	1-27

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 April 1999

Date of mailing of the international search report

07/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00223

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 872447	A	NONE	
EP 0194112	A	10-09-1986	
		AT 52915 T	15-06-1990
		AU 599585 B	26-07-1990
		AU 5388786 A	04-09-1986
		CY 1724 A	06-05-1994
		DK 90086 A	29-08-1986
		FI 860847 A, B,	29-08-1986
		GR 860549 A	24-06-1986
		HK 83893 A	20-08-1993
		IE 58943 B	01-12-1993
		JP 1965813 C	25-08-1995
		JP 6099306 B	07-12-1994
		JP 61210031 A	18-09-1986
		PH 25455 A	01-07-1991
		PT 82117 A, B	01-03-1986
		US 4956359 A	11-09-1990
		AU 599312 B	19-07-1990
		AU 5388886 A	04-09-1986
		CA 1294274 A	14-01-1992
		DK 36893 A	29-03-1993
		DK 90186 A	29-08-1986
		GR 860531 A	24-06-1986
		IN 162808 A	09-07-1988
		JP 1965814 C	25-08-1995
		JP 6099386 B	07-12-1994
		JP 61205254 A	11-09-1986
		PH 25525 A	24-07-1991
		PT 82118 A, B	01-03-1986
		US 5183902 A	02-02-1993
		US 5151418 A	29-09-1992
		US 5068231 A	26-11-1991

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

To:

HOWARD, Paul Nicholas et al.
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE

Date of mailing
(day/month/year)

0 4. 05. 00

Applicant's or agent's file reference
P018623WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/00223

International filing date (day/month/year)
22/01/1999

Priority date (day/month/year)
23/01/1998

Applicant
CEREBRUS LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Hebert, W

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P018623WO	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/00223	International filing date (day/month/year) 22/01/1999	Priority date (day/month/year) 23/01/1998	
International Patent Classification (IPC) or national classification and IPC C07D205/04			
Applicant CEREBRUS LIMITED et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 09/07/1999	Date of completion of this report 0 4. 05. 00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seelmann, I Telephone No. +49 89 2399 7480 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00223

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-37 as originally filed

Claims, No.:

8-27 as originally filed

1-7 as received on 29/10/1999 with letter of 28/10/1999

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 24-27 (industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00223

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00223

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claim 24 to 27 does not satisfy Rule 67(1)(iv) PCT, since it relates to a method for treatment of the human/animal body.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. PRIOR ART

The document cited in the International Search Report

D1: GB 872 447 A (LEPETIT S.P.A.) 12 July 1961

D2: EP-A-0 194 112 (ROBINS CO INC A H) 10 September 1986 & US
4 956 359 A cited in the application

has been considered for the examination procedure.

2. NOVELTY

The subject-matter of claims 1 to 27 meets the requirements of Article 33(2) PCT. D1 discloses i.a. 1-Carbamyl-3-phenylazetidine, however, substituted aryl groups in the R¹ position are not known from the prior art.

3. INVENTIVE STEP

The subject-matter of Claims 1-27 does not fulfil the requirements of Article 33(3) PCT for the following reasons.

The closest state of the art for the present application is represented by D1. D1 discloses

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00223

structurally similar compounds having the same qualitative properties.

Therefore, the problem underlying the present application cannot be seen in the provision of further novel derivatives, because the proposed solution would be seen as obvious.

In view of the extremely close structural relationship to the compounds of D1 it is considered that the man skilled in the art would regard the new compounds of this application as being obvious alternatives to the known compounds. Further support arises with respect to the prior art document D2, which would motivate a man skilled in the art to extend the teaching of D1 to molecules with further substituents especially to the structural analogues of the compounds disclosed in D2.

Therefore, the problem underlying the present application should be seen in the provision of new derivatives having unexpected properties over those of the closest prior art compounds (D1). The applicant has provided the result of a comparative test between the compound of example 20 of the present invention and 1-carbamoyl-3-phenylazetidine, demonstrating an unexpected effect on which the inventive step can be based.

However, terms such as "aryl", "alkyl" and the like without any specification of the carbon or heteroatom content as well as the expression "substituted" can, in general, not be allowed under Article 33(3) PCT because it can never be demonstrated by even a great number of experimental results that in fact all theoretically possible compounds would solve the problem, i.e. would lead to compounds having the alleged activity. Moreover, such a term allows any possible structure leading to compounds which, in fact, do not solve the actual problem, such as other pharmacophoric, unstable or toxic groups, e.g. the term aryl would include the highly carcinogenic benzpyrenes. Finally, substituted could also mean substituted with any molecule of any other application also claiming "substituted" compounds.

It should be noted, that the term "addition compounds" could comprise subject-matter, which cannot be allowed under Article 33(3) PCT, cf. Item VIII.

4. INDUSTRIAL APPLICABILITY

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00223

For the assessment of the present claims 18 to 22 and 24-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

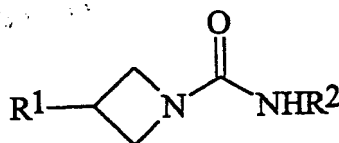
Certain observations on the international application

The term "addition compounds" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

Compound Nr. 63 of the invention described on page 34 does not fall within the scope of Claim 1, because the aryl is not substituted. This inconsistency between the claims and description leads to a doubt concerning the extent of the protection afforded by the claims, thus rendering the claims unclear, contrary to Article 6 PCT.

CLAIMS

1. A compound of formula (1)



(1)

5

wherein

R¹ is substituted aryl; and

R² is hydrogen or alkyl;

and pharmaceutically acceptable addition compounds thereof.

10

2. A compound according to claim 1 wherein R¹ is selected from substituted phenyl and substituted naphthyl.

3. A compound according to claim 1 or 2 wherein R¹ has 1, 2 or 3 substituent groups.

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4. A compound according to any preceding claim wherein R¹ is substituted with one or more substituent groups selected from halo, trifluoromethyl and tertiary-butyl.

20

5. A compound according to claim 4 wherein said halo groups are selected from chloro and fluoro.

6. A compound according to claim 1, 2, 3, 4 or 5 wherein R¹ is a meta- or para-substituted phenyl group.

25

7. A compound according to claim 1 wherein R¹ is selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

AMENDED SHEET